REMARKS

Applicants herewith amend claims 1 and 25, and cancel claim 26. Claims 12-23 have been withdrawn. Claims 1, 4, 5, 7, 9, 11, 24 and 25 are pending for examination.

Entry of the foregoing amendment is respectfully requested.

Applicants acknowledge with appreciation the telephonic interview with Applicants' attorney on June 4, 2009, and the helpful comments offered by the Examiner, summarized below. This Reply is Applicants' earnest effort to resolve the outstanding issues raised by the Examiner and advance the prosecution of this application.

Summary of the Examiner Interview

Applicants' attorney and Examiner Royds discussed the Final Action dated April 14, 2009, and the Section 112, first paragraph, (new matter) rejection and the Section 102 rejection over the Palermo *et al.* reference. Applicants' attorney pointed out additional disclosure in the application (the Examples, for example) to overcome the Examiner's new matter rejections. The Examiner maintained that Palermo discloses all of the structure and function recitations of the composition claims. The product-by-process claims were also discussed. The Examiner suggested additional "structure" be recited in the claims to distinguish over the prior art. Applicants' attorney suggested proposed wording that the Examiner indicated would reflect progress in the prosecution, and would be considered if included in an amendment. The Examiner suggested that Applicants show that the Palermo compositions do not have the dissolution resistance-on-crushing property as claimed. Applicants noted that Palermo discloses broad classes of different types of sustained release compositions, and no specific example other than the use of the Oxycontin® placebo to demonstrate the Palermo claimed invention, which is based on the concept of opiod antagonist co-dissolution, as opposed to Applicants' dissolution inhibition concept. The Examiner stated that it was Applicants' choice to select an example from the Palermo *et al.* reference. No agreement was reached

Summary of the Claimed Invention

Applicants' invention provides an abuse-resistant composition comprising microspheres that contain micronized particles of a water soluble active ingredient, susceptible to user abuse, which particles are coated, or surfaced "wetted", in a water insoluble material, and which particles are dispersed within an matrix of said water insoluble material, which water insoluble material is elastic and present in the microspheres in an "abuse-reducing" amount such that the aqueous dissolution-inhibiting function of said matrix material is preserved despite being subjected to mechanical stress, such as crushing, prior to contact with an aqueous environment (such as ingestion or contact with nasal mucous membranes), which stress would otherwise act to accelerate the aqueous release of the active from prior art abusable compositions.

Discussion of the Amendment

Claim 1 has been amended to reflect the language from Applicants' application as quoted by the Examiner in the Examiner's Action.

Amended claim 1 now more precisely defines the abuse-resistant controlled-release pharmaceutical composition, as comprising "microspheres comprising water insoluble matrix material ". Exemplary support is found at paragraph 0031:

> [0031] The preferred pharmaceutical compositions include microspheres that comprise a matrix of pharmaceutically acceptable water insoluble material.

Claim 1 further defines that "said discrete particles (1) comprise *micronized* particles of active water soluble compound having surfaces that are wetted with *a coating of said water insoluble matrix material* and (2) *are distributed throughout said microsphere within a matrix of said water insoluble matrix material*..."(italics added).

Exemplary support for "micronized" is found in original claim 17, and in the Examples 1-6, while exemplary support for "distribution throughout the microsphere with a matrix ..." is found at paragraph 0030.

> [0030] A preferred abuse-resistant composition according to the present invention comprises a matrix, throughout which the surface coated particles are distributed. In a special embodiment of the present invention, the material used to coat the surface of the particles comprises the matrix in which the particles are distributed.

Amended claim 1 further states that "said matrix is elastic and present in an abuse-reducing amount such that crushing, compressing, fracturing, tumbling, rolling, or milling of said compositions including said microspheres before coming in contact with an aqueous environment increases the aqueous dissolution of said active water soluble compound in said microspheres by less than about ... ."

Exemplary support for "abuse reducing amount" is found at paragraph 0029:

> [0029] The particles of the compounds subject to potential abuse are surface coated in an *"abuse reducing amount"* if the amount of surface coating material is sufficient, when administered by at least one manner of potential abuse other than the manner by which the composition or dosage form is intended to be administered, to prevent or diminish the occurrence of the pharmacological effects of the abusable substance or to significantly delay the onset of these effects. If an attempt were made to abuse the composition by administration through some other portal, such as by inhalation or intravenous routes, the surface coating material would prevent the occurrence of the abuse inducing effect. (Italics added).

Exemplary support for the "elastic" property of the matrix material is found at paragraphs 0058 and 0101:

> [0058] ... In alternative embodiments in which low cross-linked polymers or viscoelastic polymers are used as the matrix, the tenacity of the composition is due to the *elasticity of the matrix*. (Italics added).

> [0101] The matrix material appears to be very closely associated with the drug particle surface, wetting the drug particle surface, and is not simply admixed with the particles. Each drug particle can be viewed as being individually encapsulated by matrix material, independent of the presence of any third encapsulating component. The matrix can

> serve the encapsulating function itself. In addition, the grinding appears to only disturb the initial dissolution delay function of the microspheres. It also suggests that the matrix material retains its *elastic-like* nature through the manufacturing process. (Italics added).

Exemplary support for "aqueous environment" is found in original claim 12 and paragraphs 0028 and 0062:

> [0028] Microsphere compositions including such organic salts and prepared according to the present process are capable of linear release in an aqueous environment ... .
>
> [0062] ... a pharmaceutical composition that when subjected to stress does not increase substantially the immediate release of said compound in an aqueous environment.

Amended claim 25 is dependant on claim 1 and incorporates the recitations of cancelled claim 26, as well as being rewritten to conform closely to the sections of Applicants' disclosure quoted by the Examiner. Applicants have been careful to recite the steps of (1) forming the surface-wetted particles by pressure pulse treatment of a dispersion of active water soluble compound particles in a water insoluble fluid matrix of said coating material and (2) forming microspheres by spraying the flowable dispersion of particles formed in step (1) into a chilling zone maintained at a temperature below the solidification temperature of said coating material. Exemplary support is found at paragraph 0062, 0063, and 0065:

> [0062] The present invention also relates to the process for the manufacture of the present microspheres. The present sustained release pharmaceutical compositions having a reduced potential for abuse may be prepared by applying a pressure force to a mixture comprising particles of a compound having a potential for abuse and a water insoluble material thereby resulting in surface coated particles and incorporating the resulting surface coated particles into a pharmaceutical composition that when subjected to stress does not increase substantially the immediate release of said compound in an aqueous environment.
>
> [0063] A particularly preferred method is wherein the aforesaid pressure force is applied to a dispersion of said particles in a flowable

water insoluble medium.

> [0065] A special embodiment of the present invention forms microspheres from the surface-coated particles by the process of spraying, into a chilling zone maintained as a temperature below the solidification temperature of the water insoluble fluid matrix material, a flowable dispersion of active particles in the water insoluble fluid matrix.

Exemplary support for the water insoluble coating material being the same as the water insoluble fluid matrix is found at paragraph 0030:

> [0030] A preferred abuse-resistant composition according to the present invention comprises a matrix, throughout which the surface coated particles are distributed. *In a special embodiment of the present invention, the material used to coat the surface of the particles comprises the matrix in which the particles are distributed.* (Italics added).

Applicants respectfully submit that NO NEW MATTER is added by this amendment.

Discussion of the Examiner's Section 112 Rejection

Claims 1, 4, 5, 7, 9, 11, 25 and 26 (cancelled) stand rejected under 35 USC Section 112, first paragraph, as failing to comply with the written description requirement.

The Examiner points to the following added limitations of the claims:

(1) crushing, compressing, fracturing, tumbling, rolling, or milling of said compositions including said microspheres *before coming in contact with water*... (claims 1 and 9);

(2) does not substantially modify the dissolution rate of said *active water soluble compound* thereafter (claims 1 and 9);

(3) *wherein a pressure-pulse is applied to a flowable mixture of said coating material and said active water soluble compound to form a pressure-treated matrix* (claim 25); and

(4) *wherein said pressure-treated matrix is spray cooled to form microspheres* (claim 26).

Limitation (1), "prior to coming in contact with water":

Applicants amended claim 1 to recite "aqueous environment" in place of "water" to more precisely define Applicants' invention. Applicants' specification clearly discloses the application of mechanical stress to the composition of the claimed invention in at least two situations:

(a) *prior* to ingestion or administration to a human subject (see paragraphs 0014 and 0019[1]), and

(b) in the dissolution experiment of Example 7[2].

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1 [0014] The abuse potential that this invention is intended to reduce is the abuse potential associated with the illicit, nonprescription or recreational use of a narcotic composition and the use of the compositions of this invention by other modes of administration such as *the injection or inhalation of a crushed composition otherwise intended to be administered in intact form*. (Italics added)

[0019].... If an attempt were made to abuse the composition, in order to rapidly obtain the abuse inducing effect, for example *by crushing the dosage form and ingesting the composition or administering it through some other portal, such as intravenously*, the surface coated particles of abusable substance would inhibit any substantial increase in compound solubilzation and the occurrence of the abuse inducing effect. (Italics added)

2 Crushing Dissolution Comparison

[0097] Microsphere compositions including water-soluble drug and prepared using the methods described in the above Examples are ground (stressed) using a mortar and pestle. Stressed and unstressed samples are examined microscopically and tested for drug release rates. Comparisons are made between the two prepared samples.

[0098] The microspheres are subjected to three different degrees of crushing.

[0099] The ground samples exhibit deformed and fractured microspheres with a distribution from fine to large fragments. Some intact microspheres continue to be present in the mildly crushed sample. The unground samples are spherical and uniform (as per the -20 +40 mesh fraction taken) as originally manufactured.

[0100] Dissolution of the water-soluble active ingredient from ground and unground samples is determined.

The ground sample is characterized by a two-phase release rate, including an initial burst phase of short

In both instances, a person of ordinary skill in the art would clearly recognize that the crushing action is conducted prior to the crushed material being contacted with (a) the water-containing membrane of the body, oral, nasal or otherwise, or (b) an aqueous dissolution medium ("Dissolution of the water-soluble active ingredient from ground and unground samples is determined"), both examples of an "aqueous environment".

Limitation (2), the dissolution rate of said *active water soluble compound* thereafter.

Applicants submit that any person of ordinary skill in the art would clearly recognize that the only ingredient in Applicants' claimed composition that is of dissolution interest is the active water soluble compound. Notwithstanding this self-evident fact, Applicants clearly disclosed the two-phase nature of the dissolution rate of the active water-soluble compound in Example 7:

> [0100] Dissolution of the *water-soluble active ingredient* from ground and unground samples is determined. The ground sample is characterized by a two-phase release rate, including an initial burst phase of short duration, followed by a second release phase, which is constant over the remaining test period. The unground sample is characterized by a single phase, constant release rate over the entire test period without a burst period. The drug release rates for the ground samples following the burst period, and the unground sample are very similar. Greater crushing shows only a small increase in the burst with additional stress, while the rate of release remained the same thereafter. (Italics added)

Limitations (3) and (4), pressure pulse treatment and spraying.

While this basis for rejection may be moot in view of Applicants' amendments, Applicants direct the Examiner's attention to Examples 1-6, which clearly exemplify the use of the pressure-pulse process to make the microspheres recited in the pending composition claims,

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duration, followed by a second release phase, which is constant over the remaining test period. The unground sample is characterized by a single phase, constant release rate over the entire test period without a burst period. The drug release rates for the ground samples following the burst period, and the unground sample are very similar. Greater crushing shows only a small increase in the burst with additional stress, while the rate of release remained the same thereafter.

including the steps of subjecting a flowable dispersion of particles of active water soluble compound in a water insoluble coating material, forming a flowable dispersion that is subjected to pressure pulse treatment to form a pressure-treated mixture, which is sprayed onto a chilled area to form microspheres.

Applicants submit respectfully that the claims as amended are fully supported by the written description of Applicants' disclosure and request respectfully that the Section 112 rejection of the claims be withdrawn.

Discussion of the Examiner's Art Rejection

Claims 1, 4, 5, 7, 9, 11, and 25 stand rejected under 35 USC Section 102(b) over US Patent No. 6,228,863 (*Palermo et al.*). Applicants respectfully traverse the Examiner's rejection.

Claim 1 now incorporates the structural recitations of an abuse-resistant composition containing (1) microspheres of, (2) micronized particles of active water soluble compound (3) having surfaces wetted with a coating material dispersed in an (4) elastic matrix of said coating material (5) in an "abuse reducing amount".

Applicants' invention frustrates the abuser by setting up a formulation barrier that inhibits aqueous dissolution in the first instance, and prevents the abuser from achieving a "high" by the common method of crushing the composition for immediate release through nasal membrane absorption or otherwise.

Palermo *et al.* teach, in general, many different types of sustained release compositions, but focus on frustrating the drug abuser's attempts at extraction of abusable drug by requiring a second extraction step to eliminate a co-dissolved opiod antagonist. Nowhere do Palermo *et al.* disclose or suggest a means for retarding the initial aqueous extraction of the active opiod if the composition is crushed, milled or otherwise mechanically stressed before ingestion into the body. Nowhere does Palermo et al. disclose that discrete micronized particles of active compound are

surface-wetted with water insoluble material and dispersed in a microsphere matrix of the same material that is elastic and present in an "abuse reducing" amount.

The Examiner maintains that Applicants' claimed invention of an abuse-resistant composition that is capable of frustrating an abuser's crushing attempts to achieve the immediate release of the abusable compound is present somewhere in Palermo *et al.*, but has not identified where Palermo *et al.* specifically teach such composition. Palermo *et al.* do disclose individual ingredients useful in preparing Applicants' claimed composition, as well as general methods for creating a myriad of sustained release compositions, but Palermo *et al.* do not suggest that such ingredients be combined in the structure and manner defined in Applicants' claims, or that Applicants' claimed composition could result in abuse resistance *per se*, for example without the use of the Palermo *et al.* opiod antagonist.

In the Final Action, and during the telephone interview with Applicants' attorney, the Examiner placed the burden on Applicants to show that a composition disclosed in Palermo *et al.*, a composition which Applicants may choose, does not have the properties of Applicants' claimed invention.

Applicants believe the best evidence that Palermo *et al.* do not disclose compositions of the present claimed invention is to show that OxyContin® tablets do not exhibit the "abuse resistant" properties of the present claimed invention. OxyContin® tablets comprise ingredients identified in Palermo *et al.* for formulation as sustained release compositions. The inactive ingredients contained in OxyContin® 20 mg tablets are listed in the left hand column of the table below, and references to the Palermo *et al.* disclosure of such ingredients for use in sustained release compositions are shown in the right hand column of the table:

OxyContin® Inactive Ingredients	**Palermo *et al.* Reference**
ammonio methacrylate copolymer	(col. 16, lines 37-41)
hypromellose (hydroxypropyl methylcellulose) and stearyl alcohol,	(col. 21, lines 13-19, 24-25, col. 12, line 64)

lactose, magnesium stearate, polyethylene glycol 400, titanium dioxide, and talc	(col. 12, lines 34-43)
povidone (polyvinylpyrrolidone)	(col. 12, line 37)
sodium hydroxide, sorbic acid, (preservatives)	(col. 12, line 40)
triacetin	(col. 17, line 49-57)

The inactive ingredients comprising OxyContin® tablets are described in the Patient Insert of attached Exhibit B, and are substantially the same as described in Table 7 of US Patent No. 5,508,042, cited in Exhibit B at page 27, and in the FDA "Orange Book" listing for OxyContin® tablets.

The OxyContin® patient insert warns that crushing the OxyContin® tablet is dangerous and results in ***rapid release*** of oxycodone. See the black box warning on page 1 of Exhibit B.

> **OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

To demonstrate the quantitative nature of this "rapid release', the Examiner's attention is directed to Exhibit A, which is a copy of US Patent Publication 2009/0011016 ('016 patent"), and which discloses an experiment measuring the dissolution properties of OxyContin® tablets before and after rough crushing (pliers crushing–not fine mortar and pestle crushing disclosed by

Applicants). The results are shown in Table 26 reproduced below and in Figure 11[3], shown in footnote 3 below.

[0245] The results obtained for dissolutions in the pH 6.8 medium are given in following Table 26 and in FIG. **11**.

TABLE 26

	OxyContin® 20 mg batch 122810			Oxycodone 20 mg XCOX 5726		
Time (h)	Whole tablet	Tablet cut in half	Tablet in pieces	Whole tablet	Tablet cut in half	Tablet in pieces
0.5	35.9	50.8	61.0	1.3	8.6	26.7
1	47.1	62.8	73.4	3.7	15.0	36.5
2	60.5	75.2	85.4	10.7	28.2	51.5
3	69.4	82.3	91.6	17.3	39.4	62.2
4	76.2	87.0	95.4	24.9	49.7	70.4
6	86.0	92.9	99.0	41.7	64.8	81.9
8	92.8	96.5	100.3	55.8	75.3	88.8
12	100.7	99.4	100.7	75.7	88.1	95.9
16	103.4	100.1	100.5	87.7	94.7	99.2
20	103.9	99.4	99.5	95.3	98.4	100.7
24	—	98.2	99.2	100.4	100.5	101.5

3 The left-most curves on this '016 patent graph depict the data for the reference Oxycontin® tablets, which from right to left show the dissolution profiles for intact Oxycontin® tablets (triangle), cut Oxycontin® tablets (diamonds), and crushed Oxycontin® tablets (squares).

Figure 11

Dissolution profiles of tablets conforming to the invention(« QD ») and tablets of the reference product Oxycontin® (ref) at pH 6.8, for whole tablets, tablets cut in half, or crushed (« in pieces »)

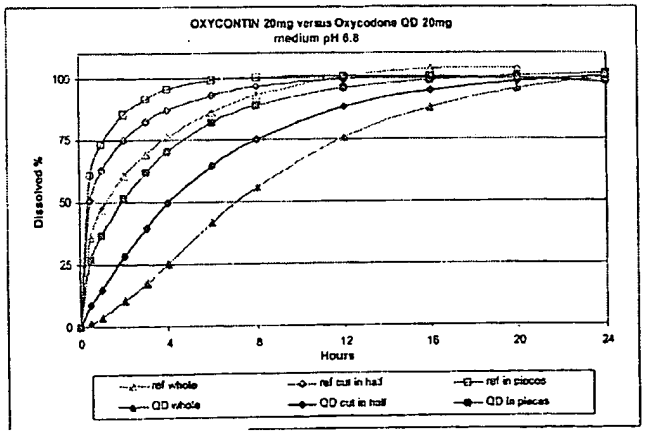

Table 26 shows that after one hour, 73.4% of oxycodone is dissolved from the crushed OxyContin® tablet in contrast to only 47.1% of oxycodone dissolved from the intact OxyContin® tablet. This is an increase of 26.3%, almost twice the maximum of 15% increase required by Applicants' claim 1. (Applicants note that this percentage increase would have been greater had the '016 patent applicants chosen to crush the OxyContin® tables with a mortar and pestle instead of crushing with pliers only).

Applicants submit respectfully that the dissolution comparison published in the '016 patent demonstrates clearly that Palermo *et al.* do not disclose, explicitly or inherently, sustained release compositions that include the physical-chemical properties required by Applicants' amended claims. Applicants further submit that Applicants' burden of proof to show that Palermo *et al.* neither disclose nor suggest all the elements of the present claimed invention is hereby met, and request that the Section 102 rejection of the claims be withdrawn.

Applicants submit that the claims as amended distinguish structurally, functionally and patentably over the art cited by the Examiner.

A favorable action on the merits is requested respectfully. If the Examiner is not prepared to withdraw the art rejections and allow the application, Applicants specifically request that the Examiner enter the amendments so that this application may be placed in better condition for appeal.

Respectfully submitted,

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